Remarks:

Claim Objections

The informalities discussed in the Claim Objections section of the Office Action mailed April 18, 2006 have been corrected.

In claim 1, line 3, a comma has been added after 'stimulus'.

In claim 2-23, a comma has been added after the recitation of the parent claim.

The preamble to claim 1 has been re-written as suggested by the Examiner.

Applicant respectfully asserts that the Claim Objections have been overcome and respectfully requests reconsideration.

Claim Rejections 35 USC 112

Applicant has incorporated the limitation "signal transduction from stimulus-receptor interactions" into all claims. The claims are no longer directed toward all events, but only a specific subset dealing with receptor activation.

Applicant respectfully disagrees with the Examiner that the Specification teaches "measuring the impedance of said cells in some *undisclosed* media within culture wells using several different electrical currents...". In paragraph [0021], applicant explains the experimental procedure that they used, including the plating, rinsing, and experimental media.

Applicant respectfully disagrees with the Examiner's statement "At no point, however, do applicants exemplify creating a database with the data in Figures 4-12, comparing data from a test cell expressing an unknown receptor or a test cell contacted with a ligand of unknown function to said database, and determining which, if any, of the pathways exemplified in Figures 4-12 are activated in said test cell." Applicant has removed the term 'database' from the claim set to clarify applicant's technology. The parameter graphs displayed in Figures 4-12 (and discussed in paragraphs [022-024]) present the patterns that are produced using this analysis

method and the patterns to which unknown ligands and unknown receptors are compared to characterize the stimulus-receptor interaction (displayed in Figures 13-14). The claims as amended teach the comparison of parameterized electrical property value changes for known pathways (which we have found to be consistently characteristic for G-protein coupled receptors and Protein Tyrosine Kinase Receptors) to parameterized changes in value for unknown stimuli or receptors. Support for this amendment can be found in paragraph [024].

Step (f) of Claims 1 and 12 no longer requires "parameter sets of known messenger pathways". The method taught in the claims does not require that a test cell be "cultured under conditions identical to those disclosed in the specification" (as suggested by the Examiner) but teaches how to characterize a stimulus-receptor interaction through the use of changes that, after parameterization, are characteristic of specific receptor responses.

Claims 1-23, 36, and 37 have been amended or deleted to clearly and particularly point out and distinctly claim the subject matter applicant regards as the invention.

The requirement that "a value" of an electrical property be measured has been specified. The value being measured is that of an electrical property of the electric circuit comprising cells after exposure of the circuit to at least one frequency of the electromagnetic spectrum. Claims 1 and 12 have been amended to clarify the placement of the cell within an electrical circuit and the measurement of a value of an electrical property of the circuit. Frequency refers to an aspect of the electromagnetic spectrum which will be applied to the system. Support for the amendments can be found in Paragraph [0022].

Applicant respectfully notes that the applicant does not understand the confusion regarding the limitation " receptor having a known receptor type and a known messenger pathway". The claim set excludes receptors for which the experimenter does not know the receptor type or messenger pathway. Applicant requests that the Examiner call the applicant to discuss the confusion regarding this limitation.

Again, applicant respectfully notes that applicant does not understand the confusion regarding the limitation of Claims 1 and 12, step (b). The time point "corresponding to" a time period immediately prior to addition of a stimulus is the definition of the reference time point, as discussed in paragraph [013].

Claims 1 and 12 has been amended to clarify that the cell receptor is being stimulated by the stimulus in step (b).

Claims 1 and 12, step (c) hav been amended to clarify that the stimulus is being added to the electrical circuit comprising a cell such that the stimulus is able to interact with the receptor (as suggested by the Examiner).
Steps (d) and (e) of Claims 1 and 12 have been amended (via the amendment of step (a)) to note that the measurement occurs at selected time points during a selected time period. Proper antecedent basis has been given to the term "time point".

In Claims 1 and 12, step (f) has been amended to point out the particular comparisons required to classify stimulus-receptor interactions.

Because Claims 1 and 12 have been clarified, applicant respectfully requests reconsideration of claims 3-6, 8, 10-11 and 13-14, 16-20, and 22 under 35 U.S.C. 112, second paragraph. Claims 36 and 37 have been deleted and the electrical circuit concept integrated into independent claims 1 and 12.
Amendments to Claims 1 and 12 have allowed Claims 2 and 15 to be deleted. Support for this amendment can be found in original claims 2 and 15 and in paragraph [001] of the specification.

Claim 3 has been amended to clarify the electrical property groupings.
Claims 7 and 21 have been deleted.
Claims 9 and 23 have been deleted.
Claims 10, 11, 13, and 14 have been amended to clarify their relationship to Claims 1 and 12.
Claims 10 and 11 use the parameterized changes in value for known messenger pathways

generated in claim 1 to characterize an unknown stimulus (Claim 10) and an unknown receptor type (Claim 11). Claims 13 and 14 use the parameterized changes in value for known messenger pathways generated in Claim 12 to characterize an unknown stimulus (Claim 13) and an unknown receptor type (claim 14).

Applicant respectfully asserts that the Claim Rejections under 35 USC 112 have been overcome and respectfully requests reconsideration.

Claim Rejections 35 USC 101

Applicant respectfully asserts that the claims have patentable utility and that the Examiner has misinterpreted the claimed method. The Examiner wrote:

> "The claims have been interpreted as being drawn to a method comprising measuring an electrical property (in some cases, impedance) of a cell expressing a known receptor, contacting said cell with a known stimulus (in some cases, a ligand to the receptor), observing changes n the electrical property, and comparing said changes to data sets from cells in which known messenger pathways are activated in order to determine which receptor is active in the cell. The claims, in short, appear to describe a method for determining the active receptor with a cell expressing a known receptor; such a method is not useful, since the claims require that the cells express a known receptor (claim 1, step a), so a person practicing said method would know before carrying out the steps which receptor is activated."

Applicant respectfully agrees that the method comprises measuring an electrical property (in some cases, impedance) of a circuit comprising cells expressing a known receptor, contacting the circuit with a known stimulus (in some cases, a ligand to the receptor), and observing the changes in the electrical property. The applicant has amended the claims to clarify that the changes in the electrical property are parameterized and the parameterized values are assigned to a known stimulus/receptor interaction class. The claims do not describe a method for determining the active receptor for a cell expressing a known receptor. Claims 1 and 12 describe

a method for mathematically characterizing the interaction of a known receptor and a known stimulus, so that later (in claims 10, 11, 13, and 14), the mathematical characterization can be used to classify the response of either unknown receptors or unknown stimuli.

The Examiner further wrote:

> "Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Situations that require carrying out further research to identify or reasonably confirm a "real world" context of use do not define a substantial utility. See M.P.E.P. 2107.01 (l)(B). In this case, the cited claims appear to be drawn to a method of establishing a database that could at some point be used to determine what receptor is active in a cell with unknown receptors or in a cell contacted with a ligand whose effect is unknown, as described in claims 10, 11, 13, an 14 which are not included in this rejection, since they are drawn to identifying some unknown property of a cell, receptor, or ligand. Without these limitations, however, the cited claims cannot be considered to have substantial patentable utility."

The applicant respectfully disagrees and notes that the applicant has clarified the claims' utility in the amended claim set. The applicant has amended the claims to clarify that what was meant by "database" was a set of parameterized values, but applicant did not mean to imply that the applicant would establish an actual database of values or that an actual database was required to practice the claims. The claims now more clearly teach that the parameterized changes in electrical value that were assigned to the known stimulus interaction with the known receptor are what the applicant uses to determine which receptor is active in a cell with unknown receptors or in a cell contacted with a ligand whose effect is unknown (as described in claims 10, 11, 13 and 14).

Applicant respectfully asserts that the Claim Rejections under 35 USC 101 have been overcome and respectfully requests reconsideration.

Claim Rejections 35 USC 103

Claims 1-23,36, and 37 were rejected under 35 USC 103(a) as being unpatentable over Wegener et al. (1999, European Journal of Physiology 437:925-934) taken in view of Rigaud et al. (1995, Physiological Measurment16: A15-A28).

Applicant respectfully agrees with the Examiner that Wegener et al. teach culturing bovine aorta endothelial cells (BAEC) in a monolayer, analyzing said cells with electric cell-substrate impedance sensing (ECIS), adding isoproterenol or alprenolol to the culture medium, and conducting ECIS on the treated cells. Applicant also agrees with the Examiner's assertion that Wegener et al. do not teach the range of frequencies recited in claims 5 and 19. Rigaud et al. do not teach analyzing numerous cell types with ECIS at numerous frequencies. Rigaud et al. is not analyzing cells, but instead using an "impedance cell" to analyze tissue samples. Rigaud et al. note, in Section 2.2 Tissue Samples, that the experiments were conducted using tissue: "Five hundred samples of five kinds of tissue were excised form 13 sheep, 15 min after the animals had been sacrificed." Furthermore, Rigaud et al. are not using ECIS. Wegener et al., on page 926, first paragraph, define ECIS: "With this experimental approach, the cells are cultured directly onto small gold-film electrodes (diameter 250μm) that are evaporated onto ordinary culture dishes and therefore serve simultaneously as growth substrate and measuring electrode." The essential element of ECIS is discussed in the same paragraph: "According to a theoretical model provided by those authors, the total impedance of the cell-covered electrode is determined basically by the capacitances of the cell membrane, the resistance between adjacent cells and the distance between the basal cell surface and the electrode." ECIS does not apply to tissue (which is what was used by Rigaud et al.) and it does not apply to tissue inserted into a cylindrical tube with electrodes inserted in a hole midway along the tube length (as used by Rigaud et al., Section 2.1 Experimental set-up). Wegener et al. also note that "The present data demonstrate the AC impedance technique as employed here allows precise quantification of the electrical tightness and capacitance of macrovascular endothelial cell layers." Wegener is correlating the cell layer resistance to the impedance with his work. The tightness and capacitance of macrovascular endothelial cell layers cannot be tested using whole tissue as used by Rigaud et al. Rigaud et al. state clearly in their Experimental Results Section (Section 3.) that "Each plot approximately

represents a depressed arc of a circle and is thus in accordance with the well known frequency response of living tissues..".

Rigaud et al. are not using their experimental method to characterize tissue (and certainly not to characterize cells, since they are not working with cells). Rigaud, as suggested by the Examiner, is not teaching parameterizing the data from ECIS experiments and comparing the data from the various cell types to each other to obtain additional characterization data for a particular cell. Again, Rigaud is not using ECIS or cells. Rigaud et al., in their data analysis experiments, are not comparing various cell types, but instead Rigaud is comparing data from the literature with their experiments to determine if muscle tissue measurements were performed longitudinally or transversely to the orientation of the muscle fibers. The determination of tissue orientation is not the same as cellular stimulus-receptor characterization (Section 4.1. Tissue group homogenization).
Applicant respectfully asserts that the Examiner has not established a case of Prima Facie Obviousness and that it would not have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the method of Wegener et al. (which requires conducting ECIS on cells to prove the advantages of single-frequency measurements) with the method of Rigaud et al. (which requires passing a current through tissue held in a cylindrical tube (utilizing a non-ECIS system and method)) to determine the orientation of the known tissue type). Applicant respectfully requests reconsideration.

Applicant also respectfully disagrees with the Examiner's assertion that: "A person of ordinary skill in the art would have had a reasonable expectation of success in conducting the method of Wegener et al. using the range of frequencies of Rigaud et al. because Rigaud et al. teaches that ECIS may be carried out across a range of frequencies to produce a data set." Rigaud is not using ECIS, but instead using a common system to apply current through tissue (not cells). Furthermore, after comparing multiple-frequency (frequency scan mode) with individual frequency measurements, Wegener et al. teach against using a range of frequencies, and instead work to find a single-frequency technique to define their cellular response: "As mentioned above, the only parameter of the equivalent circuit that changes upon β-adrenergic stimulation of

BAECs is the overall resistance of the cell layer R_{cl}. Therefore, it is also possible to follow changes in R_{cl} by simply measuring |Z| at one defined frequency instead of recording complete impedance spectra. *This single frequency technique is of immense advantage with respect to the time resolution of the measurement, reducing the latter from about 2min to 1s.*" (page 929, β-Adrenergic stimulation of BAECs: single-frequency measurements section). Wegener et al. continue to support the single-frequency impedance technique on page 930, first paragraph. The skilled artisan would *not* have been motivated to conduct the method of Wegener et al. using numerous frequencies, as asserted by the Examiner, when Wegener clearly teaches the "advantage" of single frequency measurements and teaches against the use of multiple frequency measurements.

Co-Pending Applications

Applicant has no co-pending U.S. applications that set forth a similar subject matter to the present claims. Applicant has several issued patents and abandoned applications that are in a related field of study, but that do not claim a similar subject matter to the present claims:

Patent No. 6,287,874 entitled "Methods for Analyzing Protein Binding Events," filed August 2, 1999 and issued September 11, 2001;

Serial No. 09/687,456 entitled "System and method for detecting and identifying molecular events in a test sample," filed October 13, 2000 (now abandoned);

Serial No. 60/248,298 entitled "System and method for real-time detection of molecular interactions," filed November 13, 2000 (now abandoned);

Serial No. 09/775,718 entitled "Bioassay device for detecting molecular events," filed February 1, 2001 (abandoned);

Patent No. 6,586,946 entitled "System and method for detecting and identifying molecular events in a test sample using a resonant test structure," filed February 1, 2001 and issued July 01, 2003;

Serial No. 60/268,401 entitled "A system and method for characterizing the permittivity of molecular events," filed February 12, 2001 (now abandoned);

Serial No. 60/275,022 entitled "Method for detecting molecular binding events using permittivity," filed March 12, 2001 (now abandoned);

Serial No. 60/277,810 entitled "Bioassay device for Detecting Molecular Events," filed March 21, 2001 (now abandoned);

Conclusion:

In view of the amendments and remarks set out above, it is submitted that this application is now ready for allowance. Applicant respectfully request reconsideration of the claimed matter.

If Examiner Barnhart should believe that prosecution of this application can be expedited by discussion of any issue, the Examiner is invited to contact the undersigned at any of the numbers set out below.

Respectfully submitted,

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